REMARKS

Entry of the Amendment and reconsideration of the claims in view of the following Remarks is respectfully requested.

Claim 19 has been amended. Support for the amendment can be found throughout the specification, including page 10, line 24 to page 11, line 19; Table 1 and page 32, lines 21-22.

Specification

The specification was objected to because of informalities. Specifically, the Examiner states that no SEQ ID NOs are provided for the sequences recited at page 4, lines 5, 8, and 17; page 26, line 9; and page 28, line 19. Applicants have amended the specification to identify these sequences. Withdrawal of the objection is requested.

35 U.S.C. 112, first paragraph

Claims 19-27 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Applicants traverse this rejection.

The amended claims are directed to a method of constructing a library of structurally-constrained peptides comprising preparing a plurality of peptides having a scaffold for β-turn display, each peptide comprising a presented turn sequence and a scaffold comprising first and second opposite strands with a defined backbone hydrogen-bonding pattern, each strand comprising at least two Trp residues at non-hydrogen-bonded positions, and each trpzip domain consists of the amino acid sequence WX_1W, wherein X_1 is independently Thr or an amino acid selected from the group consisting of H, V, I, F, Y and W; and wherein the Trp residues from each trpzip domain form a cross-strand pair without any disulfide bond, wherein the presented turn sequence comprises random amino acids.

As an initial matter, Applicants note there is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. See *Guidelines for Examination of Patent Applications under 35 U.S.C. § 112, first paragraph "Written Description Requirement" IIA.*

Furthermore, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by reduction to practice, by

disclosure of relevant identifying characteristics such as structure, physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or a combination of these characteristics. *MPEP 2163 II. A.3.(a)ii).*

When the above factors are carefully weighed, the specification clearly describes the claimed subject matter in a manner reasonably conveying to one of skill in the art that Applicants had possession of the claimed invention.

The Examiner contends it is unclear how the claimed synthesis is accomplished, since the method recites only a single step. Applicants submit they have described many methods for preparing the peptides as claimed, including synthesis and phage display. See page 11, line 20 to page 11, line 19. Applicants have exemplified preparation of a number of different peptides using peptide synthetic methods. (See Example 1, page 25.)

The Examiner also asserts it is unclear what is being synthesized in the absence of any recitation of a primary sequence for the peptides of the claimed libraries, such as the kind and length of the random amino acids in the turn sequence.

Applicants disagree, and assert that the specification does provide guidance concerning the length of the random amino acids in the presented turn sequence. The Examiner's attention is respectfully directed to page 6, lines 11-19, which discloses examples of particular embodiments where the presented turn sequence comprises at least 4 amino acids or at least 6 amino acids. The specification also discloses particular embodiments where the peptide scaffold has a minimum length of 10 amino acids, with 4 amino acids comprising the presented turn sequence and three amino acids on each end of the scaffold to serve as flanking strands (lines 13-16). The specification also discloses preferred embodiments where the peptide scaffold comprises 12, 14, 16, 18, or 20 amino acids, and a preferred embodiment wherein the scaffold is no more than 20 amino acids in length (lines 17-19).

Applicants also submit that many beta-turn sequences are known in the art, such that the claims need not be limited to peptides comprising turn structures having a specific primary sequence. One of ordinary skill in the art would readily recognize that the peptides generated by the claimed methods are useful for stably presenting a variety of beta-turn sequences. Moreover, this is a method claim and the presented turn sequence may comprise random amino acids.

The Examiner also asserts the claims contain too many undefined variables, such as the position of the Trp-Trp cross-strand, the number of Trp-Trp cross-strands, or the types of constraints imposed on the beta-turn structure scaffold. The Examiner contends the specification describes the synthesis of only a single species wherein Thr is varied to create the library.

Applicants respectfully disagree, and submit the specification provides sufficient guidance regarding the variables of the peptides, and discloses multiple species that are representative of the genus recited by the claims. (See Table 1, page 34.) Nevertheless, Applicants have amended the claims to speed prosecution of the case. The amended claims recite that the first and second opposite strands of the scaffold each comprise a trpzip domain, wherein the trpzip domain consists of the amino acid sequences WX_1W, such that each strand comprises at least two Trp residue at non-hydrogen-bonded positions, wherein the Trp residues of each trpzip domain form a cross-strand pair without any disulfide bond, and wherein X_1 is independently Thr or an amino acid selected from the group consisting of H, V, I, F, Y, and W.

Applicants submit that the peptides of the library recited by the amended claims are amply described by the specification. The disclosure specifically exemplifies the synthesis of nine peptides that comprise trpzip scaffolds comprising the WXW motif recited by the amended claims (see Example 1, Example 2, and Table 1). The scaffolds of the invention are shown to stabilize the turn sequence EGNK (trpzips 1 and 2), the beta-hairpin peptide gb1 taken from the IgG-binding domain of protein G (trpzips 4-9), and the turn sequence EPNK (trpzip3). These synthesized trpzip peptides present turn sequences having varying lengths, including 4 amino acids (trpzips 1-3), and six amino acids (trpzips 4-9), and have varying overall peptide lengths of 12 amino acid residues (trpzips 1-3) or 16 amino acid residues (trpzips 4-9). The trpzips were used to present a variety of turn sequence types, including type I turns, type I' turns, and type II' turns (see Table 1).

Additionally, the synthesized trpzip peptides represent multiple species of the WXW cross-strand zipper, wherein X is varied to include His or Val (see Table 1). Applicants further describe that amino acids I, F, Y, and W can be substituted for H, V, or I. Applicants disclose that each of trpzip peptides 1-9 having variations as X successfully presented a stabilized turn sequence (see page 28, line 19 through page 33, line 7). Indeed, the specification discloses that trpzip peptides of the invention presenting the gb1 beta-hairpin peptide were more stably folded

than wild type gb1 (page 30, line 27 through page 31, line 6; page 30, lines 11-22; and page 31, line 28 through page 32, line 2).

For the foregoing reasons, Applicants submit that the claims are fully described, because the disclosure exemplifies the synthesis of multiple species of peptides that are representative of the genus recited by the claims, and shows the ability to stabilize multiple beta-turn sequences. The Applicants have met the standard for written description provided by the Written Description guidelines by identifying the structure, physical properties, chemical properties, and functional characteristics of multiple peptides of the invention, including 1) the identity of their primary sequences, 2) their three-dimensional structure, and 3) their functional ability to stabilize beta-turn sequences, using NMR and CD spectroscopy. The Applicants have also coupled these characteristics by disclosing correlations between function and structure, through comparisons of the structure and beta-turn stabilizing abilities of trpzip peptides having different lengths and/or different amino acid substitutions at positions X_1 and X_2 (see, for example, page 29, lines 11-24; page 30, lines 9-13; page 30, line 27 through page 31, line 22; and page 32, lines 3-29).

The Examiner also contends the specification does not describe the use of the library obtained by the claimed methods in terms of the utility requirement.

Applicants assert, however, that the disclosure does in fact describe the use of libraries obtained by the methods as claimed. The specification discloses that beta-turns have been implicated as important sites for molecular recognition in biologically active peptides, such that peptides containing conformationally-constrained beta-turns are particularly desirable, and that the mechanisms by which beta-turns are stabilized is a subject of considerable interest (page 3, lines 10-20).

In light of the importance of beta-turns, the present invention provides methods for generating peptide libraries that can display small peptides with stable hairpin beta-turn structures (page 5, lines 26-29). These libraries are useful to screen for novel peptides capable of binding to a target molecule, and that are useful as diagnostics or therapeutics (page 6, line 20 through page 7, line 3). Therefore, the disclosure provides a specific, well-established use for the claimed methods.

Additionally, Applicants respectfully direct the Examiner's attention to the existence of commercially available peptide libraries. Applicants assert that such libraries belie any

suggestion that methods for generating libraries of structurally constrained peptides as claimed would lack utility. Morphosys, Inc., for example, provides Human Combinatorial Antibody Libraries (HuCAL) for the *in vitro* generation of highly specific and fully human antibodies. Multiple pharmaceutical and biotechnology research companies have incorporated Morphosys' libraries into their R&D processes, including Bayer, Biogen, Bristol-Myers Squibb, Centocor/Johnson&Johnson, Immunogen, Oridis, Roche, Schering, and Xoma. Thus, libraries of peptides can clearly possess significant utility in the area of biotechnology and pharmaceutical research.

In addition, the U.S. Patent & Trademark Office has routinely granted patents to libraries of compounds. *See, e.g.*, U.S. Pat. No. 6,482,591 (claims to synthetic conformationally-restricted probe libraries), and U.S. Pat. No. 6,475,806 (claims to libraries of fusion proteins). Applicants submit the USPTO routinely finds sufficient utility for, and grant patents on, claims to libraries of compounds wherein the utility lies in the ability to screen the library for compounds that can bind to specific target molecules.

For at least the foregoing reasons, Applicants respectfully submit that the disclosure provides ample description for the claims, because the specification reasonably conveys to one of ordinary skill in the art that Applicants were in possession of the invention at the time of filing. Withdrawal of the rejection is therefore requested.

35 U.S.C. 112, second paragraph

Claims 19-27 were rejected under 35 U.S.C. 112, second paragraph as indefinite. Applicants traverse this rejection.

The Examiner contends it is unclear if the library of peptides is contained within the presented turn sequence, what parts of the turn sequence are randomized, and whether the library is different from the recited plurality of peptides.

Applicants have amended the claims for clarity and to address the Examiner's concerns. Applicants submit the amended claims clarify that the library is the recited plurality of peptides, that the peptides of the library comprise a presented turn sequence and a peptide scaffold. The portion of the peptide that is randomized is the presented turn sequence. Withdrawal of the rejection is therefore requested.

The Examiner also states that the phrase "zipper-like motif" is indefinite. Although Applicants disagree, and submit that this phrase is clearly defined at page 9, lines 18-21, the amended claims do not recite this phrase. Withdrawal of the rejection is requested.

35 U.S.C. 103

Claims 19-27 were rejected as obvious over Cochran et al. WO 0077194). Applicants traverse this rejection.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met, namely: (1) the references when combined must teach or suggest all of the claim limitations; (2) there must be a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of skill in the art to modify the reference or combine the reference teachings; and (3) a reasonable expectation of success. Applicants submit not all of these requirements have been met because, in the least, the reference does not disclose all of the claim limitations, and there is no reasonable expectation of success in modifying the reference to obtain the presently claimed invention.

The Examiner contends that Cochran et al. discloses or at least suggests a method of synthesizing a library of peptides containing W-W cross-strands. The Examiner asserts it would have been within the ordinary skill in the art to pick and choose the specific claimed residues taught in the generic formula. Applicants respectfully traverse this rejection.

Applicants submit that Cochran et al. does not disclose all elements of the claims. For example, Applicants' claims recite "wherein the trp residues form a cross-strand pair without any disulfide bond." The Cochran et al. reference, by contrast, states that "the peptides of the invention are cyclized via disulfide bonds between two cysteines within the peptide sequences" (page 3, lines 6-10). Cochran does not disclose or suggest any advantage to structurally constrained peptides that do not have a disulfide bond as recited by the claims.

Indeed, and as the Examiner acknowledges, Cochran discloses that the disulfide bond results in the peptide adopting a cyclic form in solution that facilitates the formation of a beta-hairpin scaffold, and asserts that disulfide cyclization is helpful to constrain the structure of peptides (page 9, 19-23). As a result, one of ordinary skill in the art would not be motivated by

the teachings of Cochran to generate structurally constrained peptides comprising the scaffold recited by the claims, in the absence of a disulfide bond.

The Examiner states that Cochran et al. discloses that disulfide bond geometry was initially thought incompatible with the cross-strand geometry of hairpins. Under an obviousness analysis, however, the Examiner must consider the prior art reference as a whole. *MPEP 2141 II.* The Cochran et al. reference as a whole shows that 1) disulfide bonds are compatible with hairpin stability, 2) peptides described therein do have disulfide bonds, and 3) that there are specific advantages to scaffolds having disulfide bonds. Thus, one of skill in the art reading the reference as a whole would not be motivated to remove disulfide residues from the disclosed peptides.

The Examiner asserts that the experiments disclosed by Cochran are primarily directed to turn sequences in the absence of cysteines. Applicants respectfully disagree with the Examiner's characterization of Cochran. Applicants submit that the working examples of Cochran are directed to the synthesis and analysis of disulfide-constrained beta-hairpins (see, for example, page 23, lines 19-20; page 27, lines 21-23 and Table 2).

Thus, Applicants submit that for at least these reasons, Cochran et al. does not teach or suggest Applicants' claimed invention.

In addition, in the present case, it was surprising that a peptide scaffold having at least two Trp-Trp cross-strand pairs was soluble, given that in some embodiments one-third of the residues are Trp residues. It was thought that such a high level of Trp would decrease the solubility of a peptide in solution. Moreover, the presence of at least two Trp-Trp cross-strand pairs in the scaffold could have been less stabilizing due to the intra-strand interaction of the two Trp residues.

For the foregoing reasons, Applicants assert that claims 19-27 are patentable over Cochran. Withdrawal of the rejection is respectfully requested.

Claims 19-27 were rejected as obvious over Robinson et al. (US 6,878,804) in view of Floudas et al. (US 2003/0036093). The Examiner asserts that Robinson discloses a method of constructing a library of structurally constrained peptides, and that large surface protein interfaces contain hotspots of binding energy enriched in Trp, Tyr, and Arg. The Examiner acknowledges that Robinson does not disclose a Trp zipper-like motif, but contends that Floudas

provides motivation to choose Trp-Trp as a cross-strand zipper-like motif in the method of Robinson. Applicants respectfully disagree.

As the Examiner acknowledges, Robinson does not disclose structurally constrained peptides comprising at least two Trp-Trp cross-strand pairs. Nor does Robinson teach or suggest that such peptides can or should comprise a peptide scaffold comprising first and second opposite strands each comprising a trpzip domain consisting of the amino acid sequences WX_1W, respectively. Rather, Robinson discloses beta-hairpin loop mimetics that are fixed to a template, as shown in Formula I, column 1. Therefore, Robinson uses template fixation to constrain peptides into a cyclic formation (column 6, lines 19-20). As a result, Robinson provides no motivation to generate structurally constrained peptides using the Trp-Trp cross-strands recited by the claims in place of the template fixation techniques.

Applicants submit that Floudas does not remedy these deficiencies of Robinson. Floudas nowhere teaches or suggests a structurally constrained peptide comprising at least two Trp-Trp cross-strand pairs, or that such peptides can or should comprise a peptide scaffold comprising first and second opposite strands each comprising a trpzip domain consisting of the amino acid sequences WX_1W, respectively. Therefore, one of ordinary skill in art would not be motivated by the teachings of Floudas to use Trp-Trp cross-strand pairs, and flanking strands consisting of the amino acid sequences WX_1W, respectively, in the method of Robinson.

Moreover, even assuming the existence of a motivation to combine the teachings of Robinson and Floudas, one would not obtain the presently claimed methods, nor have any reasonable expectation of success in doing so. As discussed above, neither Robinson nor Floudas teach or suggest that a constrained peptide for displaying a beta-turn sequence can or should comprise a peptide scaffold comprising first and second opposite strands each comprising a trpzip domain consisting of the amino acid sequences WX_1W, respectively.

Neither reference teaches or suggests that a stable peptide scaffold comprising at least two Trp-Trp cross-strand pairs could be formed. In some embodiments, the peptide scaffold structures as claimed are presenting turn sequences in a relatively short peptide (see page 6, lines 1-5) and there would be no reasonable expectation of success that the sequence of opposite strands could be modified while still maintaining the stability of a peptide scaffold.

In addition, it was thought that forming a peptide scaffold with multiple Trp residues would decrease solubility of the scaffold. It was surprising that a peptide scaffold having at least two Trp-Trp cross-strand pairs was soluble, given that in some embodiments one-third of the residues are Trp residues. Moreover, the presence of at least two Trp-Trp cross-strand pairs in the scaffold could have been less stabilizing due to the intra-strand interaction of the two Trp residues.

For at least these reasons, Applicants respectfully submit that claims 19-27 are nonobvious over Robinson in view of Floudas, alone or in combination. Withdrawal of the rejection is therefore requested.

Interview

Applicants request an interview with the Examiner and her supervisor. Applicants request that the Examiner contact Applicants' representative upon receipt of these papers.

SUMMARY

Applicants submit that all claims are in condition for allowance, and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative at the telephone number listed below, if the Examiner believes that doing so will advance prosecution.

Respectfully submitted,

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